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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/478,621	01/05/2000	Stephen E. Epstein	674522-2001	1917

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EXAMINER	
JIANG, DONG	
ART UNIT	PAPER NUMBER
1646	13

DATE MAILED: 05/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

B-S

Office Action Summary	Application No.	Applicant(s)	
	09/478,621	EPSTEIN ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/18/02 & 3/1/02* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 8-17* is/are pending in the application.

4a) Of the above claim(s) *12-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED OFFICE ACTION

Applicant's amendment in paper No. 10, filed on 18 January 2002 is acknowledged and entered. Following the amendment, claims 1, 3-5, 9, and 10 are amended, and claims 2, 6, and 7 are canceled. Applicant's supplemental amendment in paper No. 11, filed on 01 March 2002 are acknowledged. Following the amendment, the new claims 12-17 are added.

Currently, claims 1, 3-5, and 8-17 are pending.

Newly submitted claims 12-17 would belong to the Group II invention in the restriction requirement indicated in the Office Action, paper No. 6, mailed on 27 February 2001, at page 2. They are directed to an invention that is independent or distinct from the originally elected invention, the Group I invention, for the reasons of record in the Office Action, paper No. 6, at page 2. Therefore, they are withdrawn from prosecution as being drawn to a non-elected invention.

Accordingly, claims 1, 3-5, and 8-11 are under consideration in the present Office Action.

Withdrawal of Objections and Rejections:

The objection of claims 1 and 8-11 is withdrawn in view of applicant's amendments.

The rejection of claims 1, 3, 4, 8, and 9 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendments.

Objections and Rejections under 35 U.S.C. 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, and 9-11 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 remains indefinite for reciting the limitation "the vessel maturation inducer" in line 1. There is insufficient antecedent basis for this limitation in the claim. Further, as indicated

in the last Office Action, paper No. 9, page 3, the term "vessel maturation inducer" is not a recognized term in the art. Therefore, it is unclear what is meant by "vessel maturation inducer" in these claims, and what agents are encompassed by this term. Applicants argue at page 5 of the response, filed on 18 January 2002 (paper No. 10), that the term is defined clearly in the specification. This argument has been fully considered, but is not deemed persuasive because, while the specification defines *an agent* which induces vessel maturation, the term "vessel maturation inducer" is not even present in the statement. Therefore, the description of an agent can not be considered the equivalent of the definition of "vessel maturation inducer".

Claim 9 remains indefinite because it is not clear what is meant by "by admixture" in line 2, and what would be admixed. Additionally, it is unclear what is the interrelationship between the parts of the kit. Are they in a container, or in separate containers or bags? As required, the interrelationships between the elements must be explicitly stated (see In re Venezia, 530 USPQ 2d 956 (CCPA 1975)).

Claim 10 remains indefinite because it is unclear what is "*inhibiting* VEGF *inhibitor*", as indicated that the protein agent is for inhibiting VEGF, not VEGF inhibitor.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, and the dependent claims 3-5, and 8-11 remain rejected under 35 U.S.C. 112, first paragraph, as they are not enabled for the limitation of "preventing" atherosclerosis and/or restenosis as recited in claims 1, 8 and 9, for the reasons of record in the last Office Action, paper No. 9, at pages 5-6.

Applicants argument, filed on 18 January 2002 (paper No. 10) has been fully considered, but is not deemed persuasive for reasons below.

At pages 8 and 9 of the response, the applicant argues that the specification describes how such prevention should be carried out, and that one of ordinary skill in the art would be able to determine the susceptible individuals via familial determination or routine procedures, such as

ECG. This argument is not persuasive because the issue is not how to administer the medication, rather, the issue is identifying the susceptible individuals. While familial determination may be helpful in making an educated conjecture in certain diseases, it can not predict with any certainty as to which individual would or would not have a given disease. Additionally, it has not been established in the art that familial determination is useful in predicting restenosis. With respect to ECG test, it can only detect the stenosis *after* the pathological changes have happened, therefore, it is not useful in identifying the susceptible individuals who have not developed the pathological change. Therefore, one of ordinary skill in the art would not be able to select those individuals for the treatment in order to *prevent* restenosis and/or atherosclerosis. While the instant composition may be helpful in *reducing* restenosis and/or atherosclerosis, such administration can not ensure that the patient would not develop atherosclerosis or restenosis. As there is no decisive means to predict who would be developing the conditions without the treatment, and such preventative effect has not been shown, the asserted utility of *preventing* the diseases is not enabled.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, and 8-11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Inoue et al. (Circulation, Nov. 1998, 98(20): 2108-16), and Maisonpierre et al. (Science, July 1997, 277:55-60), in view of Kendall et al. (US 5,712,380), and Asahara et al. (Circ. Res., 1998, 83: 233-240), for the reasons cited in the last Office Action, paper No. 9, at pages 6-8.

Applicants argument, paper No. 10 has been fully considered, but is not deemed persuasive for reasons below.

At pages 10 and 11 of the response, applicants list teachings missing in each individual reference cited, and argue that none of the cited references discloses, suggests, or motivates to practice the claimed invention. This argument is not persuasive because applicant's arguments are against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, even though none of the cited references by itself discloses the claimed invention, suggestion or motivation to do so can be found based on combinations of references, which teach that VEGF is involved in the process of atherosclerosis and neointimal angiogenesis, that the coronary occlusive lesions have extensive neovascularization (by Inoue); that ang-1 and Tie2 receptor play critical roles in angiogenic outgrowth, vessel remodeling, and maturation, that ang-2 is a natural antagonist for ang-1 and the Tie2 receptor, that therapeutic manipulation of vessel growth, is likely to require simultaneous regulation of *both* the VEGF and angiopoietin systems (by Maisonpierre); that a soluble VEGF receptor would be useful as a treatment for persistent pathological angiogenesis (by Kendall); and that ang2 + VEGF promoted significantly longer and more circumferential neovascularity (by Asahara). It is logical and obvious to a skilled artisan to design a medical intervention to inhibit both ang2 and VEGF for treating atherosclerosis and/or restenosis, and to expect therapeutic effect in individuals with such conditions because the

combined teachings from these references clearly indicate the involvement of VEGF and angiopoietins in atherosclerosis and restenosis.

At page 12 of the response, the applicant further argues that VEGF system involved in the regulation of angiogenesis is a complex process, and finding modulators of VEGF does not guarantee a therapy for atherosclerosis or restenosis. While the Examiner agrees the complexicity of the VEGF system, and even more complex is the biological body as a whole, the therapies of treating diseases are developed mainly based upon simplified in vitro and in vivo (animal models) experimentations and observations because there is no way of knowing how hundreds and thousands of biological molecules interact with each other in a body. No therapy is guaranteed prior to the clinical application, and it is the *expectation* of success, not the success itself, that should be suggested by the prior art. In the instant case, the involvement of VEGF and angiopoietins in atherosclerosis and the occlusive lesions strongly suggests a therapy that antagonizes the activities of both VEGF and ang2. Further, the Examiner notes that as the claims are not limited to any particular agents, the Examiner would, if applicants argument were persuasive, be forced to apply a rejection under 35 U.S.C. 112, first paragraph, for lack of enablement.

Conclusion:

No claim is allowed.

Advisory Information:

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

DJ
5/7/02